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TITLE: Treatment of Vestibular Dysfunction Using a Portable Stimulator

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1. INTRODUCTION

Vestibular symptoms seem to be a common problem with ~20% of veterans complaining of dizziness and those with dizziness demonstrating increased risk of Motor Vehicle Accidents. To treat veterans with vestibular dysfunction we will optimize stimulation using a portable stochastic noise electrical stimulator and determine the effectiveness of subsensory electrical stimulation in a population of veterans with verified impaired vestibular function. We will perform experimental and sham stimulation on patients with impaired function to improve clinical vestibular and balance function during testing. We will assess the effectiveness of using this portable stochastic noise electrical stimulator to improve driving performance and determine what effect subsensory electrical stimulation has on vestibular function.

2. KEYWORDS

None to report

3. ACCOMPLISHMENTS

Major Goals of the Project

Major Goal 1 - Develop a portable stimulator which can be worn continuously and used to improve vestibular function (April 2014 to June 2016)

Subtask 1: Establish Project Management System/Develop Logistical Plan (April – Aug 2014)

- a. Train the current members of the team (research assistant and research engineer) on vestibular screenings, balance assessments, and electronic stimulation.
- b. Research engineer will optimize equipment and write analysis scripts for Aim 1.

Milestone #1: Establish project management system, hire and train research staff (Planned Completion Aug 2014) – 100% complete

Subtask 2: Regulatory Review and Approval Process (April – Sept, 2014)

- a. Finalize IRB paperwork including application, protocol and consent form.
- b. Submit any revisions requested by the regulatory board prior to approval.
- c. Obtaining DoD HRPO approval.

Milestone #2: Regulatory review and approval obtained (Planned Completion Nov 2014) – 100% complete

Subtask 3: Recruitment Plan (Sept 2014 – Jan 2015)

- a. Develop plan to meet recruitment goals. **(completed)**

- b. Mail IRB approved recruitment letters to Veterans seen at the WRIISC; follow up with phone calls.
(A total of 512 veterans have been contacted by phone to participate in the study, with 229 interested in participating and 144 eligible for study visits)
- c. Distribute flyers to all VA facilities and their ambulatory services including community-based outpatient clinics to publicize the study. **(completed)**
- d. Work with NJ VA Physical Medicine & Rehabilitation Department (TBI clinic) to recruit from their patient population.
- e. Contact Veteran Service Organizations for support on best way to perform outreach. **(completed)**

Milestone #3: Recruitment Plan Executed (Planned Completion Jan 2015)
– 90% Completion

Subtask 4: Development of Portable Stimulator (April 2014 – March 2016)

- a. PI to meet with Dr. Breen at University of Western Sydney to go over specifications for Portable Stimulator Design. **(completed)**
- b. Development of initial prototype design at University of Western Sydney. **(completed)**
- c. Production of first generation prototype portable stimulator at University of Western Sydney to be shipped to New Jersey for testing. **(completed)**
- d. Redesign of prototype unit at University of Western Sydney based on findings from experiments performed in New Jersey. **(completed)**
- e. Production of second generation prototype vestibular stimulators at the University of Western Sydney for further testing in New Jersey. **(completed)**
- f. Redesign of prototype unit at the University of Western Sydney based on findings from experiments performed in New Jersey. **(completed)**
- g. Production of third generation prototype vestibular stimulators at the University of Western Sydney for shipping to New Jersey for further testing. **(completed)**
- h. Redesign of third generation stimulators for fabrication of units for use in Specific Aim 2 performed at National University of Ireland Galway. **(completed)**
- i. Fabrication of 20 units based on final design specifications at the National University of Ireland Galway. **(completed)**
- j. Testing of initial fabricated units from the National University of Ireland Galway in New Jersey to ensure they are meeting required standards and creating desired improvement.
- k. Shipment of remaining units from National University of Ireland Galway to New Jersey for use in Specific Aim 2.

Milestone #4: 20 portable stimulators received (Planned Completion March 2016)
– 90% Completion

Subtask 5: Enroll subjects and conduct testing on Sub-sensory Galvanic Stimulation Study (Oct 2014 – June 2016)

- a. Screen subjects/ collect data: total of 250 subjects
 - 3 subjects per week/ 3 study visits (3 hours each)

- Vestibular testing, balance assessments
(89 subjects have been enrolled and completed study screening visit, 28 have completed the experimental trial out of 42 planned, and another 14 have been screened as having low otolith function and are being scheduled for experimental trials. Therefore we are at 42/42 necessary scheduled.)
- b. Data analysis (Post-doctoral fellow/research assistant will continually analyze data as collected).
- c. Biomedical engineer will continue to modify equipment and MATLAB analysis scripts as needed.
- d. Present/publish work.

Milestone #5: Enrolled and tested subjects (Planned Completion April 2016) – 67% Complete (28/42)

Milestone #6: Data analysis completed (Planned Completion May 2016) –67% Complete (28/42)

Milestone #7: Data presented/published (Planned Completion June 2016) – 0% Completion

Major Goal 2 – To examine long term improvement of vestibular function in veterans with electrical stimulation (April 2016 to March 2017)

Subtask 1: Examine effects of Stochastic Noise Over a 6 Week Stimulation Paradigm (April 2016 – April 2017)

- a. Screen subjects/collect data: total of 69 subjects
 - 3 unique subjects per week
 - Subjects return every 3 weeks for balance/vestibular testing
 - Subjects to wear portable stimulator over 6 week trial
- b. Data analysis
 - Analysis will be performed throughout data collection
- c. Present/publish work

Milestone #8: Enrolled and tested subjects (Planned Completion Jan 2017) – 0% Completion

Milestone #9: Data analysis completed (Planned Completion Feb 2017) – 0% Completion

Milestone #10: Data presented/published (Planned Completion March 2017) – 0% Completion

Major Goal 3 – To improve driving performance using Electrical Stimulation

Subtask 1: Effect of Improving Vestibular Ocular Reflex on Driving Function (Sept 2016 to March 2018)

- a. Initial testing and safety verification previously completed on driving simulator
- b. Institutional approvals obtained
- c. Pilot motion profiles to obtain optimal motion profiles to test role of vestibular function in driving performance

- d. Engineer will write analysis scripts to measure reaction time, stopping time and trajectory, collision avoidance and emergency braking for driving simulator to measure driving performance
- e. Engineer will develop analysis system which will track acceleration of participant and eye movements to obtain vestibular ocular reflexes while performing driving task
- f. Screen subjects/collect data: total of 69 subjects
 - 3 subjects per week
 - Complete driving simulator protocol (sham and stimulator trials)
- g. Data analysis
- h. Present/publish work

Milestone #11: Testing and safety confirmed (Planned Completion Sept 2016)
– 0% Completion

Milestone #12: IRB approval obtained (Planned Completion Dec 2016)
– 0% Completion

Milestone #13: Pilot testing completed (Planned Completion Feb 2017)
– 0% Completion

Milestone #14: Data collection completed (Planned Completion Sept 2017)
– 0% Completion

Milestone #15: Data analysis completed (Planned Completion Oct 2017)
– 0% Completion

Milestone #16: Data presented/published (Planned Completion March 2018)
– 0% Completion

ACCOMPLISHMENTS DURING THIS ANNUAL PERIOD

Major Activities

Regulatory Review and Approval Process

- a. Submitted IRB documents for revised Aim 2 protocol to include an increase in sample size (69 to 84) and an introduction of a longer testing period with stimulation (a two day stimulation protocol to a two-week period).

Major Goal 1

Subtask 3: Recruitment Plan

- a. A total of 512 veterans have been contacted by phone to participate in the study, with 229 interested in participating and 144 eligible for study visits.
- b. 89 veterans came in for the screening visit. 46 of those veterans returned for the second visit. 28 completed the study.

Milestone #3: Recruitment Plan Executed (Planned Completion August 2016) – 95% Complete

Subtask 4: Development of Portable Stimulator

- a. Redesign of a third generation prototype of the vestibular stimulator has been accomplished and is being tested at VANJ.
- b. Dr. Jorge Serrador (PI) will be traveling to Australia in May 2017 to pick up 20 portable stimulators to be used in Aim 2.

Milestone #4: 20 portable stimulators received (Planned Completion March 2016) – 90% Completion

Subtask 5: Enroll subjects and conduct testing on Sub-sensory Galvanic Stimulation Study (Oct 2014 – June 2016)

- 89 subjects have been enrolled into the study and have completed the study screening visit.
- Screening visits of 89 subjects have been fully analyzed for eligibility for stimulation visits.
- 54 subjects are eligible to return for stimulation visits.
- 28 subjects have completed stimulation testing.

Milestone #5: Enrolled and tested subjects (Planned Completion April 2016) – 67% Complete (28/42)

Milestone #6: Data analysis completed (Planned Completion May 2016) –67% Complete (28/42)

Specific Objectives for Year 3

- 1) Continued execution of recruitment plan by phone calls, posting flyers, and recruiting from VA TBI patient populations
- 2) Enrollment of subjects and data collection
- 3) Analysis of collected data
- 4) Redesign of portable stimulator based on experimental findings and initial plans for miniaturization of stimulator circuit
- 5) Fabrication of 20 portable stimulator units based on final design specifications
- 6) Continue testing using sub-sensory stimulation and analysis of data
- 7) Specific Aim 2: Examine effects of stochastic noise over a 2week stimulation paradigm

Significant Results of Year 3

- 1) Research flyers have been posted to aid in recruitment. Fourteen additional people were contacted to participate in this study with 1 people performing a phone screen.
- 2) Of the 229 phone screens, 144 were eligible to participate in the study. 89 participants came in for screening visits during this year making our total enrollment number to 89.
- 3) Overall, we have been able to analyze the screening visits of 89 participants. Of these, 45 show vestibular hypofunction and were/are able to participate in visits using stochastic noise.

- 4) A total of 28 subjects have completed stimulation visits and we are in the process of analyzing these results. Data collection using sub-sensory stimulation continues to progress.
- 5) Dr. Serrador will be traveling to Australia in May to pick up 20 portable stimulators to be used in Aim 2.

Now that we have identified 100% of the required number of Veterans with vestibular hypofunction to be test in Aim 1 we have begun the process of submitting the IRB for Aim 2.

Major Findings, Developments, Conclusions, and Other Achievements

Major Findings, Developments, Conclusions, and Other Achievements

- There are several findings that are developing out of the first specific aim data. We have found that there has been a significantly greater level of vestibular hypofunction than we originally anticipated. Figure 1 demonstrates the subjects screened so far and the associated ocular torsion.

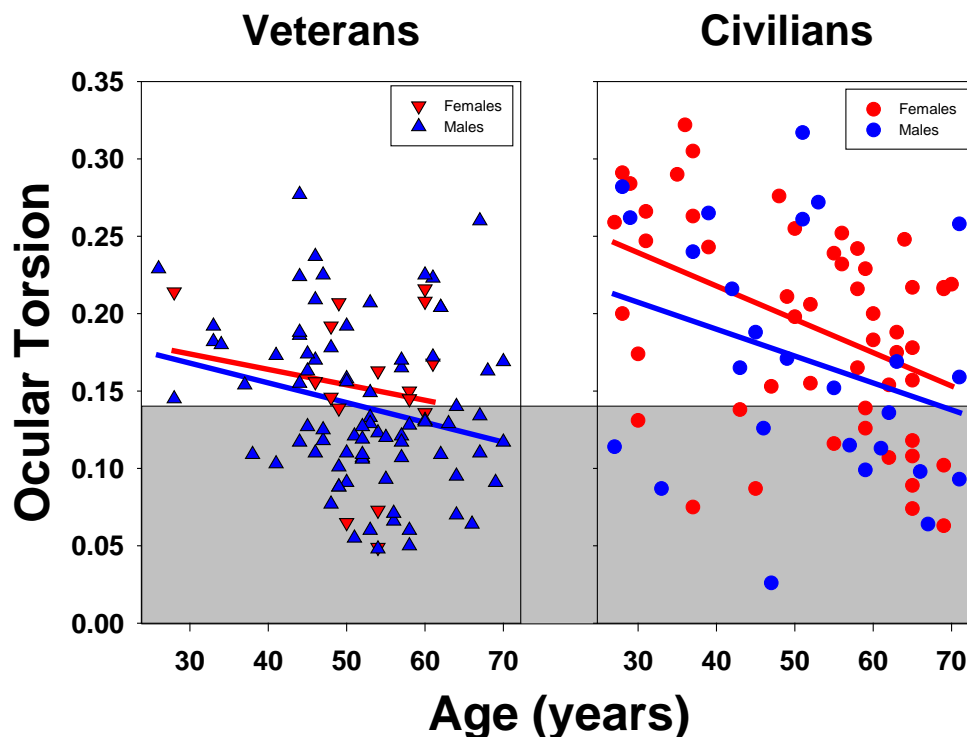


Figure 1 – Ocular torsion of veterans screened as part of Specific Aim 1 and group of civilians from previous work out of Dr. Serrador’s lab. Gray box indicates the individuals that are classified as having low otolith function. Veterans recruited into the study have a significantly lower level of vestibular function than civilians and a much greater percentage with low ocular torsion (reduced otolith function) suggesting this problem appears to be more prevalent than originally anticipated.

- Comparing the veteran data to a group of civilians of similar age that were part of a previous study the PI completed in Boston we see that the veterans have significantly lower levels of ocular torsion (Figure 2). In fact the mean values in the female and male

veterans were 0.15 and 0.14, compared to 0.20 in the female civilians and 0.17 in the male civilians. These data also indicate that female veterans may be at greater risk for vestibular hypofunction. Although larger numbers are needed to confirm this.

Comparison of Ocular Torsion in Veterans vs Civilians

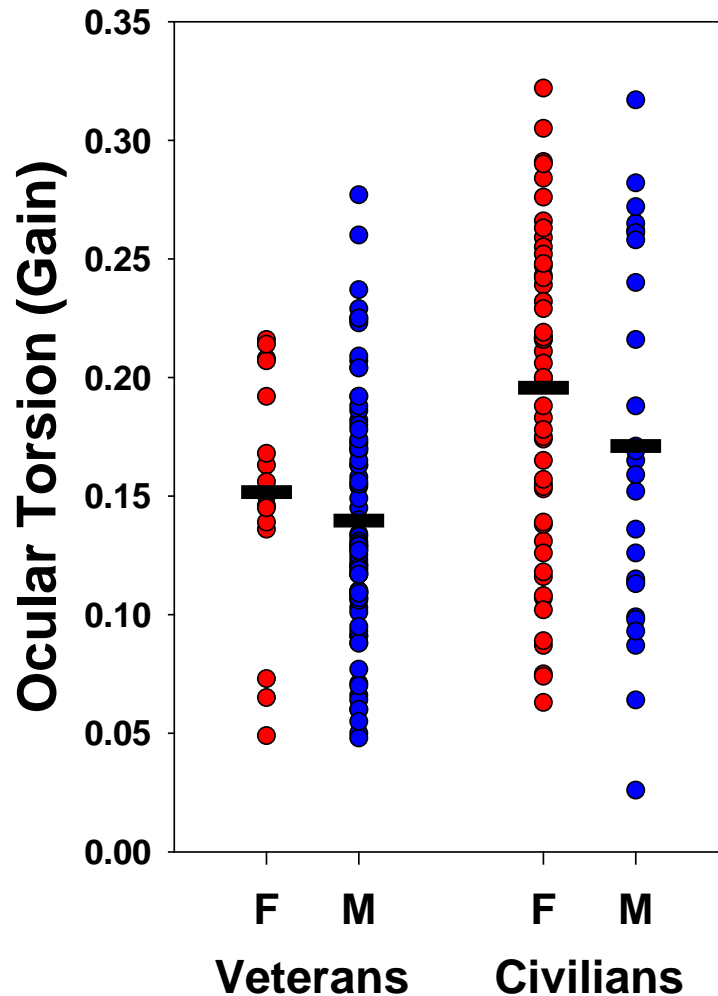


Figure 2 – Ocular torsion in veterans (left) vs civilians (right) of similar age. Note that the veterans have significantly lower ocular torsion than the civilians. These data suggest that veterans may be at risk for vestibular hypofunction. A larger epidemiologic study is necessary to confirm these findings.

- We also examined the effect of the stimulator (V1) on ocular torsion and balance function. We stimulated the veterans using a low level (subsensory) of random electrical noise with 95% of the power banded below 2 Hz. Stimulation levels were set for each individual to either 20,40,60,80 or 100% of sway threshold (level at which sinusoidal GVS at 0.1 Hz caused sway). Level chosen was based on the optimal level for that individual. Stimulation levels varied but were a mean of ± 0.20 mA (Range 0.02 – 0.62 mA).
- Examining ocular torsion we found that in the 25 (out of 30) veterans with complete data sets, that 17 of 25 showed improvement (68%). There was a mean improvement of 19% (range 2-39%) which was significant ($P < 0.05$). This is a significant finding since at the moment there are NO current treatments that are able to improve the vestibular ocular reflex of ocular torsion.

Improvement in Balance (Reduced Sway) in Veterans During Stochastic Noise Stimulation

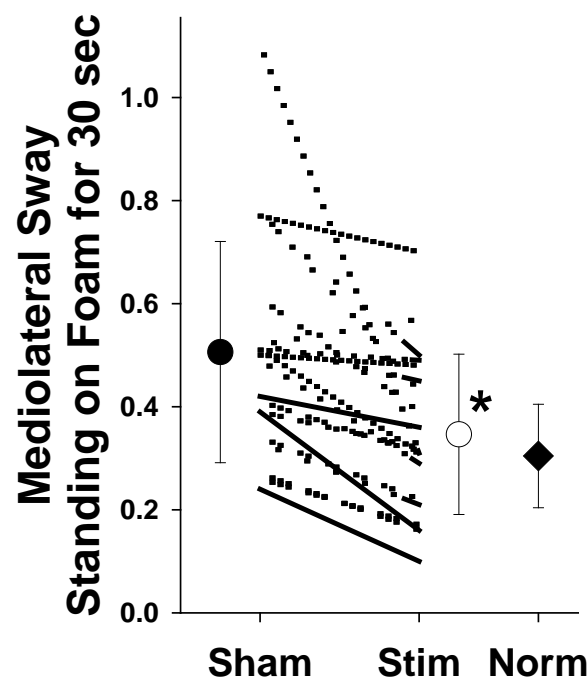


Figure 3 – Response of 14 veterans to Control (no stim) and low level random electrical stimulation (S) while performing a 30 sec static standing balance task on a force plate under four conditions: Eyes open on firm surface (EO), eyes closed on firm surface (EC), eyes open on unstable surface consisting of foam block (EOF), eyes closed on unstable surface (ECF). Traditionally it is assumed that vestibular function is more important during the trials with eyes closed, so EC and ECF. However, stimulation that improved vestibular ocular reflex did not seem to reduce sway consistently during these trials. However, sway during EOF did improve suggesting the improved vestibular input may have bolstered the sensory integration with vision to improve balance.

- We further examined the balance of individuals during sham and stim sessions at the levels used above to produce an increase in ocular torsion. Our goal was to determine if the improvement in vestibular ocular reflex would translate into an improvement in balance function. Examining the response we found that 100% of 30 participants with analyzed data. Figure 4 demonstrates that improvement. This suggests that the stimulator may be a very useful treatment for balance loss. The ability to improve balance in everyone suggests with the correct tuning, we certainly can see an effect in static balance.
- One interesting finding is that the greatest improvement occurred in the eyes open on foam block condition. In this condition the instability of standing on foam increases sway. We believe that the stimulator was most effective at this level because the increased vestibular input, provided by the stimulator, was integrated with the visual information to result in the most effective improvement in balance control.
- These data suggest that testing the effects of long term stimulation in the lab environment may be important to determine if the improvement in balance gets better with increasing time for the brain to integrate the improved vestibular signal with other sensory signals.

What opportunities for training and professional development has the project provided?

This project has provided training for all research staff to be competent at vestibular screenings, balance assessments, and electronic stimulation procedures. Our biomedical engineer has been able to develop an improved stimulator prototype under guidance of Dr. Breen.

How were the results disseminated to communities of interest?

- Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?

- 1) Continued execution of recruitment plan by phone calls, posting flyers, and recruiting from VA TBI patient populations.
- 2) Enrollment of subjects and data collection.
- 3) Analysis of collected data.
- 4) Test miniaturized units produced by Dr. Breen in lab to ensure they are ready for use in Specific Aim 2.
- 5) Continue testing using sub-sensory stimulation.
- 6) Analysis of sub-sensory stimulation data.
- 7) Begin process of gaining IRB approval for Specific Aim 2.
- 8) Develop driving simulator protocol for Specific Aim 3.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

- Nothing to Report

What was the impact on other disciplines?

- Nothing to Report

What was the impact on technology transfer?

- We are currently exploring with the technology transfer offices at both Western Sydney University and Rutgers the possibility of patenting some of the technology involved. No concrete plans have yet been made.

What was the impact on society beyond science and technology?

- Nothing to Report

5. CHANGES/PROBLEMS

- Nothing to Report

Changes in approach and reasons for change

- Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

- Now that we have identified 100% of the required number of Veterans with vestibular hypofunction to be tested in Aim 1, we have begun the process of submitting the IRB for Aim 2. There was a 9 month delay in starting Aim 1 due to delayed HRPO approval. We are continuing to make strides towards accomplishing mile stones. Based on this preliminary finding, we believe that we will still be able to reach our goals within the proposed timeframe. We will continue to review our recruitment success and analysis in the next yearly report.

Changes that had a significant impact on expenditures

- There were no changes in expenditures.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents:

Significant changes in use or care of human subjects

- No changes to use or care of human subjects to report.

Significant changes in use or care of vertebrate animals.

- No animal use research will be performed to complete the Statement of Work.

Significant changes in use of biohazards and/or select agents

- No biohazards and/or select agents will be used to complete the Statement of Work.

6. PRODUCTS

Publications, conference papers, and presentations

- Nothing to Report.

Journal publications.

- Nothing to Report.

Books or other non-periodical, one-time publications

- Nothing to Report.

Other publications, conference papers, and presentations.

- Nothing to Report.

Website(s) or other Internet site(s)

- Nothing to Report.

Technologies or techniques

- Nothing to Report.

Inventions, patent applications, and/or licenses

- Nothing to Report.

Other Products

- Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**What individuals have worked on the project?**

Name: Jorge Serrador, PhD

Project Role: PI

Nearest person month worked: 2

Contribution to Project: no change

Name: Kelly Brewer, MS

Project Role: Study Coordinator

Nearest person month worked: 9

Contribution to Project: no change

Name: Bishoy Samy, MS

Project Role: Research Engineer

Nearest person month worked: 3

Contribution to Project: no change

Name: Leslie De La Cruz, BS

Project Role: Research Assistant

Nearest person month worked: 6

Contribution to Project: performing subject recruitment, testing, data analysis.

Name: Maran Shaker, MS

Project Role: Research Assistant

Nearest person month worked: 1

Contribution to Project: performing subject recruitment, testing, data analysis.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

- Nothing to Report

What other organizations were involved as partners?

1. Organization Name: University of Western Sydney- Paul Breen, PhD

Location of Organization: Australia

Partner's contribution to the project:

- Financial support – Nothing to report
- In-kind support – Dr. Breen's salary is covered by UWS as detailed in original proposal.
- Facilities – Nothing to report
- Collaboration – Designed a novel low power stochastic noise stimulator that will be used to improve vestibular function in our patients.
- Personnel exchanges – Nothing to report
- Other – Nothing to report

2. Organization Name: National University of Ireland Galway- Gearóid Ó Laighin, PhD

Location of Organization: Ireland

Partner's contribution to the project:

- Financial support – Nothing to report
- In-kind support – Prof. Ó Laighin's salary is covered by NUIG as detailed in original proposal.
- Facilities – Nothing to report
- Collaboration – Assist Paul Breen in the design of a novel low power stochastic noise stimulator.
- Personnel exchanges – Nothing to report
- Other – Nothing to report

3. Organization Name: Azusa Pacific University- Scott Wood, PhD

Location of Organization: California

Partner's contribution to the project:

- Financial support – Nothing to report
- In-kind support – Nothing to report
- Facilities – Nothing to report
- Collaboration – Provided expertise in scientific protocol development specifically with regards to driving performance assessment.
- Personnel exchanges – Nothing to report
- Other – Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

- None

QUAD CHARTS: N/A

9. APPENDICES: None.